See article by Kane et al, p1254

# Long-Acting Injectable Antipsychotics: An Underutilized Treatment Option

*Stephan Heres, MD*



In this issue, Kane and colleagues[1] report on the efficacy of aripiprazole long-acting injection (LAI) in the treatment of an acute episode of schizophrenia. At 10 weeks of treatment, both psychopathology and functioning were improved in patients treated with aripiprazole compared to placebo, with an acceptable tolerability and safety profile. The outcomes suggest that aripiprazole long-acting is a viable treatment option for patients experiencing an acute episode of schizophrenia. Yet, the proof of aripiprazole's efficacy as a long-acting compound in this treatment scenario is only 1 lesson we learn from this important work, and in my view there are several other aspects the reader should consider.

Long-acting injections are an underutilized, yet highly efficacious, treatment option we have in helping patients who are suffering from schizophrenia. In most Western countries, the prescription rate is below 10% of all antipsychotics.[2–4] This low rate is in contrast to evidence from naturalistic studies repeatedly demonstrating lower relapse and rehospitalization rates in patients receiving LAIs compared to oral treatment.[5–7] Although some colleagues might point out that recent randomized controlled trials (RCTs)[8–10] failed to corroborate results from the naturalistic studies, a broad consensus has developed that the patients in these RCTs (ie, those who are motivated to participate in a demanding clinical trial) are most likely not representative of those we see in our everyday clinical routine (ie, patients facing compliance problems).[11]

Even less often do we find evidence based on the use of LAIs in an acute treatment setting apart from registrational trials.[12,13] Antipsychotics used in acute treatment (ie, the first days of treatment) are administered orally for a number of understandable reasons (eg, unclear response of the patient to the specific compound, flexibility in dosing, unknown individual tolerability, and perhaps avoidance of parenteral administration if the patient has poor disease insight). The problem is that this initial decision is not reassessed later in the treatment course, and patients remain on the oral formulation at discharge without further consideration of the resulting implications, most importantly critical future adherence issues.[14,15]

In clinical routine, in fact, most patients are not informed that the choice to receive a long-acting formulation of an antipsychotic even exists until they have suffered several relapses and often reached a stage of possibly irreversible chronicity or resulting deficits.[16,17] However, reports like that of Kane et al[1] remind us that LAIs could be well used as an option in the early phase of an episode with both good tolerability and efficacy depending, of course, on the individual patient and the antipsychotic compound.

Another very interesting finding of the reported study is a rarely demonstrated and often neglected facet of the side effect profile of aripiprazole. Although it is widely agreed that aripiprazole has a favorable side effect profile among other second-generation antipsychotics,[18] weight gain and the incidence of clinically significant weight gain found by Kane et al in the aripiprazole-treated patients were astonishingly high compared to those seen in both placebo-treated patients in this trial and patients in previous long-term studies with aripiprazole long-acting injections.[19,20] According to the authors, the underlying reason could be increased food intake in the inpatient setting but could also be the higher percentage of African-American patients (66% in the current study vs roughly 20% in previous studies) enrolled in this trial. Mean weight gain was numerically greater in African American participants compared to Caucasian patients. The authors interpret this finding in the context of a doubled rate in those with African ancestry of the presence of a genetic risk allele associated with antipsychotic-induced weight gain. This important finding reminds us that careful clinical monitoring of antipsychotic tolerability is necessary in all patients exposed to any antipsychotic in order to account for individual predisposition and minimize treatment-emergent side effects that could potentially lead to later poor medication adherence.

Unfortunately, the trial does not add to our knowledge about LAI treatment in an important subgroup of patients who potentially stand to benefit most from LAI treatment—those suffering from their first episode of schizophrenia. As we learned 15 years ago from Delbert Robinson and colleagues, first-episode patients' future compliance and persistence with antipsychotic treatment is highly influenced by the tolerability experienced during the initial treatment phase (and, at the same time, noncompliance is the leading risk factor for the first relapse).[21] As mentioned above, aripiprazole long-acting could be a new option offering both an acceptable side effect profile and the advantage of a long-acting formulation allowing for compliance transparency. Therefore, trials or studies targeting especially first-episode patients are needed.

***Submitted:*** *September 23, 2014; accepted September 23, 2014.*

***Corresponding author:*** *Stephan Heres, MD, Technische Universitaet Muenchen, Psychiatry, Moehlstrasse 26, Muenchen, Bavaria 81675, Germany (s.heres@lrz.tu-muenchen.de).*

*J Clin Psychiatry 2014;75(11):1263–1265 (doi:10.4088/JCP.14com09541).*

Noteworthy from a study design perspective is the methodological approach of defining week 10 as the critical time point relevant for the primary endpoint of the trial rather than the week 12 study visit at the end of the trial course. Together with rater-blinded Positive and Negative Syndrome Scale (PANSS) assessments, this aspect of the design helps limit potential rater bias and could be considered for future antipsychotic trials. Another new design feature recently used in an interventional trial[22] involved keeping both patients and investigators blinded to randomization timing and response criteria (only the ethical review board was aware of this information). In the face of consistently growing placebo response[23] and thus diminishing differences between active compounds and placebo comparators, all measures that can be taken to rule out confounders are more than relevant for facilitating valid signal detection in interventional trials.

In addition to this elaborate design aiming for limiting rater bias, from a reader's perspective one might ask for a more uniform way of reporting response in acute treatment trials in general and also in this trial. In trials published over the last decade, the threshold for response varies from 20% to 50% PANSS score reduction, and so studies remain barely comparable.[24] In the era of meta-analyses, the availability of comparable outcomes is essential for generating valid conclusions from this type of analysis. As long as we lack a uniformly accepted definition of the outcome measure "acute response to antipsychotic treatment," researchers could report the percentages of patients reaching 20%, 30%, 40%, and 50% reduction in PANSS total score in order to allow for a broader comparability between studies. Of note, the cutoff of 30% PANSS total score reduction applied by Kane et al[1] can be considered a quite sound criterion for response, while, for example, 20% is rather questionable according to corresponding PANSS/Clinical Global Impressions score reduction analyses.[25]

To return to the concern initially raised in this commentary, one might wonder whether the availability of another second-generation antipsychotic long-acting formulation will profoundly alter our current underutilization of LAIs. In view of research on treatment attitudes over the last 2 decades showing repeatedly that underutilization of LAIs derives significantly more from psychiatrists' hesitation than from patients' skepticism toward LAI drugs,[16,26,27] we should reconsider whether "shared decision making" is really occurring with regard to the choice of oral versus LAI treatment. Psychiatrists often avoid discussions about LAI use, just as they do discussions of other underutilized treatment strategies such as electroconvulsive therapy or lithium treatment. At the same time, we lack clear-cut scientific reasons why we should not make use of these effective interventions—the skepticism is not evidence-driven. As recently stated, introducing the concept of shared decision-making in its classical form has not led to its broad use in the treatment of severe mental disorders over several years, and so a modification, especially one aimed at addressing those difficult discussions with patients, could empower psychiatrists to make greater use of underutilized treatment approaches, including LAIs.[28]

In summary, the article by Kane and colleagues[1] should remind us to consider LAI as a treatment option more often in general, and also earlier in the treatment course. Nevertheless, it also reminds us of the pursuit of major efforts to overcome the underutilization of LAIs via new ways of patient-centered communication and doctors' empowerment.

***Author affiliations:*** Technische Universitaet Muenchen, Department of Psychiatry, Muenchen, Bavaria, Germany.
***Potential conflicts of interest:*** **Dr Heres** has received speaker honoraria from Janssen-Cilag, Eli Lilly, Sanofi-Aventis, and Johnson & Johnson; has accepted travel or hospitality payment from Janssen-Cilag, Sanofi-Aventis, Johnson & Johnson, Pfizer, Bristol-Myers Squibb, AstraZeneca, Lundbeck, Novartis, and Eli Lilly; has participated in clinical trials sponsored or supported by Eli Lilly, Janssen-Cilag, Johnson & Johnson, Bristol-Myers Squibb, AstraZeneca, Lundbeck, Novartis, Servier, Pierre Fabre, Pfizer, Organon, Roche, and Merck; and has received honoraria for participation in advisory boards or activities as a consultant from Lundbeck, Otsuka, Eli Lilly, Roche, Janssen, and Johnson & Johnson.
***Funding/support:*** None reported.

## REFERENCES

1. Kane JM, Peters-Strickland T, Baker RA, et al. Aripiprazole once-monthly in the acute treatment of schizophrenia: findings from a 12-week, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry.* 2014;75(11):1254–1260.
2. Nasrallah HA. The case for long-acting antipsychotic agents in the post-CATIE era. *Acta Psychiatr Scand*. 2007;115(4):260–267.
3. Sim K, Su A, Ungvari GS, et al. Depot antipsychotic use in schizophrenia: an East Asian perspective. *Hum Psychopharmacol*. 2004;19(2):103–109.
4. Ahn J, McCombs JS, Jung C, et al. Classifying patients by antipsychotic adherence patterns using latent class analysis: characteristics of nonadherent groups in the California Medicaid (Medi-Cal) program. *Value Health*. 2008;11(1):48–56.
5. Grimaldi-Bensouda L, Rouillon F, Astruc B, et al; CGS Study Group. Does long-acting injectable risperidone make a difference to the real-life treatment of schizophrenia? results of the Cohort for the General study of Schizophrenia (CGS). *Schizophr Res*. 2012;134(2–3):187–194.
6. Tiihonen J, Haukka J, Taylor M, et al. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. *Am J Psychiatry*. 2011;168(6):603–609.
7. Tiihonen J, Wahlbeck K, Lönnqvist J, et al. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. *BMJ*. 2006;333(7561):224.
8. Macfadden W, Ma YW, Thomas Haskins J, et al. A prospective study comparing the long-term effectiveness of injectable risperidone long-acting therapy and oral aripiprazole in patients with schizophrenia. *Psychiatry (Edgmont)*. 2010;7(11):23–31.
9. Rosenheck RA, Krystal JH, Lew R, et al; CSP555 Research Group. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. *N Engl J Med*. 2011;364(9):842–851.
10. Buckley PF, Schooler NR, Goff DC, et al; the PROACTIVE Study. Comparison of SGA oral medications and a long-acting injectable SGA: The PROACTIVE Study. *Schizophr Bull*. 2014.
11. Kirson NY, Weiden PJ, Yermakov S, et al. Efficacy and effectiveness of depot versus oral antipsychotics in schizophrenia: synthesizing results across different research designs. *J Clin Psychiatry*. 2013;74(6):568–575.
12. Lauriello J, Lambert T, Andersen S, et al. An 8-week, double-blind, randomized, placebo-controlled study of olanzapine long-acting injection in acutely ill patients with schizophrenia. *J Clin Psychiatry*. 2008;69(5):790–799.
13. De la Gándara J, San Molina L, Rubio G, et al. Experience with injectable long-acting risperidone in long-term therapy after an acute episode of schizophrenia: the SPHERE Study. *Expert Rev Neurother*. 2009;9(10):1463–1474.
14. West JC, Marcus SC, Wilk J, et al. Use of depot antipsychotic medications for medication nonadherence in schizophrenia. *Schizophr Bull*. 2008;34(5):995–1001.
15. Hamann J, Kissling W, Heres S. Checking the plausibility of psychiatrists arguments for not prescribing depot medication. *Eur Neuropsychopharmacol*.

2014;24:1506-1510.
16. Heres S, Hamann J, Kissling W, et al. Attitudes of psychiatrists toward antipsychotic depot medication. *J Clin Psychiatry*. 2006;67(12):1948–1953.
17. Jaeger M, Rossler W. Attitudes towards long-acting depot antipsychotics: a survey of patients, relatives and psychiatrists. *Psychiatry Res*. 2010;175(1–2):58–62.
18. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382(9896):951–962.
19. Fleischhacker WW, Sanchez R, Perry PP, et al. Aripiprazole once-monthly for treatment of schizophrenia: double-blind, randomised, non-inferiority study. *Br J Psychiatry*. 2014;205(2):135–144.
20. Fleischhacker WW, Sanchez R, Johnson B, et al. Long-term safety and tolerability of aripiprazole once-monthly in maintenance treatment of patients with schizophrenia. *Int Clin Psychopharmacol*. 2013;28(4):171–176.
21. Robinson D, Woerner MG, Alvir JM, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry*. 1999;56(3):241–247.
22. Adler L, Tanaka Y, Williams D, et al. Executive function in adults with attention-deficit/hyperactivity disorder during treatment with atomoxetine in a randomized, placebo-controlled, withdrawal study. *J Clin Psychopharmacol*. 2014;34(4):461–466.
23. Alphs L, Benedetti F, Fleischhacker WW, et al. Placebo-related effects in clinical trials in schizophrenia: what is driving this phenomenon and what can be done to minimize it? *Int J Neuropsychopharmacol*. 2012;15(7):1003–1014.
24. Leucht S, Heres S, Hamann J, et al. Methodological issues in current antipsychotic drug trials. *Schizophr Bull*. 2008;34(2):275–285.
25. Leucht S, Kane JM, Kissling W, et al. What does the PANSS mean? *Schizophr Res*. 2005;79(2–3):231–238.
26. Heres S, Hamann J, Mendel R, et al. Identifying the profile of optimal candidates for antipsychotic depot therapy: a cluster analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32(8):1987–1993.
27. Heres S, Schmitz FS, Leucht S, et al. The attitude of patients towards antipsychotic depot treatment. *Int Clin Psychopharmacol*. 2007;22(5):275–282.
28. Hamann J, Heres S. Adapting shared decision making for individuals with severe mental illness. *Psychiatr Serv*. In press.